Nutritional and metabolic aspects of the hepatorenal axis

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Diet, lifestyle, and total bilirubin: the Zutphen elderly study

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Abstract

Background. Levels of serum bilirubin, a potent endogenous antioxidant, were found to be lower in chronic disorders that are associated with increased levels of oxidative stress including diabetes and cardiovascular disease. Levels of oxidative stress are also influenced by diet and lifestyle. Little is known about the effects of diet and lifestyle on bilirubin concentrations. Therefore, our aim was to investigate the associations of the Mediterranean diet, individual food groups, and lifestyle factors such as smoking with bilirubin concentrations in elderly men without major chronic diseases.

Methods. A cross-sectional study was performed in elderly men participating in the Zutphen elderly study. Habitual alcohol and dietary consumption were assessed. Dietary patterns were studied with the Mediterranean Diet Score (MDS). Linear regression analyses were performed to determine associations of the MDS, components of the MDS, tea, wine consumption, and smoking status with bilirubin.

Results. In total, 509 male subjects were included. Median age was 71 (IQR 67–75) years. Mean bilirubin level was 7.7 ± 3.5 μmol/L. Both adherence to the MDS with more than 4 points and wine consumption were significantly associated with higher serum bilirubin concentrations (unstandardized B = 0.84, $P = 0.009$ and unstandardized B = 0.91, $P = 0.013$ respectively). Although not statistically significant, we found that tea consumption was positively associated and that smoking status was inversely associated with bilirubin concentrations in univariable analyses.

Conclusions. These findings suggest that a healthy dietary pattern like the Mediterranean diet and consumption of wine may increase bilirubin levels which could have beneficial effects on oxidative stress and oxidative stress-related diseases.

Introduction

For decades, bilirubin was believed to be a potentially toxic waste product of heme catabolism (1,2). During the last decades, however, it has been demonstrated that bilirubin is a potent endogenous cytoprotectant and antioxidant (2–4). Furthermore, decreased bilirubin concentrations might reflect increased levels of oxidative stress, which results in increased utilization of the endogenous antioxidant bilirubin (5,6). Moreover, it has been consistently shown that bilirubin concentrations were lower in patients with chronic disorders that are also associated with increased levels of oxidative stress including chronic kidney disease, diabetes, and cardiovascular disease (6).

Besides chronic diseases, lifestyle factors are also known to affect levels of oxidative stress. A major contributor to increased oxidative stress is smoking (7). Accordingly, bilirubin concentrations were found to be significantly lower in individuals who smoked, possibly as a consequence of increased utilization of bilirubin (5). In addition, diet was also found to be associated with oxidative stress. Adherence to the Mediterranean diet was found to be significantly associated with decreased markers of oxidative stress (8–10).

However, little is known about the effects of diet and lifestyle on bilirubin concentrations. Therefore, our aim was to investigate the associations of diet patterns, individual foods, and lifestyle factors such as smoking and wine consumption with bilirubin concentrations in elderly men without major chronic diseases.

Patients and methods

Study population

The population-based Zutphen Elderly Study was initiated in 1985 to collect data on diet and risk factors of cardiovascular disease in elderly men, living in a middle-sized city in the eastern part of The Netherlands. Details of the study were described previously (11). In brief, of the 1,266 men who were invited, a total of 939 (74%) men, aged 64–85 years (response rate 74%), participated in the study. Subjects with missing data on the baseline measurement of bilirubin were excluded from the analyses (n = 128, 14%). Because coronary heart disease, cardiovascular disease, and cancer increase the risk of death and may induce changes in dietary habits, 261 subjects with a history of myocardial infarction, stroke, diabetes or cancer and with complete data on dietary intake at baseline were excluded at baseline. Furthermore, because underweight can be considered as a hallmark of underlying chronic disease, 9 subjects with underweight, defined as a BMI below 18.5 (12), (n = 8) or missing data on body mass index (BMI, n = 1) were excluded. Of the remaining 541 subjects, 32 were excluded because of missing data on food consumption. Finally, 509 subjects were eligible for analyses. The

study was approved by the Medical Ethics Committee of the University of Leiden, The Netherlands and adhered to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Definitions and measurements

In 1985, information on patient characteristics was collected including height, weight, systolic and diastolic blood pressure, information on occupation, physical activity, use of medication, smoking status, history of myocardial infarction, stroke, diabetes mellitus, and cancer. BMI was calculated as weight (kg) divided by height (m) squared. Systolic and diastolic blood pressure were measured twice by using a random-zero sphygmomanometer while participants were in the supine position. The mean values of the 2 blood pressure measurements are presented. Information on occupation was collected by a self-administered questionnaire. Two occupational groups were defined: professionals and men with administrative jobs (high socioeconomic status [SES]); small business owners and manual workers (low SES). Physical activity was assessed with a questionnaire and summed into the total physical activity in minutes per week. Medication use was reported to the examining physician by the participant and coded to the ATC system. Information on smoking habits was collected using a standardized questionnaire (13). For the current study, men were divided into current smoker or non-smoker. The estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (14).

Baseline serum total bilirubin, glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP) were measured on a SMAC (Technicon, Tarrytown, NY) in the Central Clinical Chemical Laboratory of the Academic Hospital in Leiden, The Netherlands. Non-fasting serum total cholesterol and high density lipoprotein (HDL) were determined enzymatically with the CHOD-PAP mono-testkit (Boehringer, Mannheim, Germany) in the Standardized Lipid Laboratory of Wageningen University, The Netherlands.

Assessment of food and alcohol consumption

The habitual alcohol and dietary consumption were assessed by dieticians, using the cross-check dietary history method (15), adapted to the Dutch situation. This method provides information about the habitual food and alcohol consumption, based on consumption in the month preceding the interview. The interview consisted of three

steps. First, information about the usual food consumption pattern during weekdays or weeks was collected. This was checked by collecting data on the average consumption of foods during a day or a week. The second check consisted on the quantity of foods bought for the whole family during a week. Consumed foods were encoded according to the Uniform Food Encoding System (16) and foods were categorized into 22 food groups.

Dietary patterns were studied with the modified Mediterranean Diet Score (MDS). The MDS was calculated according to Trichoupoulou et al. (17). First, median dietary intake was calculated of the following components of the MDS: ratio of mono-unsaturated to saturated fat; legumes, nuts, and seeds; grains; fruit; vegetables; fish; meat; dairy products. For the components ratio of mono-unsaturated to saturated fat (M/S); legumes, nuts, and seeds; grains; fruit; vegetables; and fish, a 1 was assigned to subjects whose consumption was at least as high as the median. The remaining subjects were assigned a 0. For the components meat and dairy products, a 0 was assigned to subjects whose consumption was at least as high as the median. A 1 was assigned to the remaining subjects. This was done because the consumption of meat and dairy products was low in the traditional Mediterranean Diet (17). Maximal adherence to the MDS renders a score of 8 points. Low adherence to the MDS was defined as 4 points or less and high adherence as more than 4 points.

Statistical analysis

Baseline characteristics of the study population were calculated according to tertiles of bilirubin. Normally distributed variables are presented as mean ± standard deviation (SD), skewed distributed variables are presented as median (interquartile range [IQR]), and categorical variables are given as number (percentage). Differences in baseline characteristics across tertiles of bilirubin were tested using the ANOVA test for normal distributed data, the Kruskal-Wallis test for nonnormal distributed data, and the Chi-square test for categorical variables. Differences in bilirubin between men with a high or a low MDS and components of the MDS were tested with a t-test. A t-test was also applied to determine differences in bilirubin for the 2 levels of groups of diet and lifestyle components. Correlations between the MDS, smoking, consumption of wine and tea were investigated with Fisher's exact test. Finally, to assess the independent associations of bilirubin and its correlates, multivariable linear regression analysis was used and stepwise backward elimination was applied. Statistical analyses were performed using SPSS (version 22.0, SPSS Inc. Chicago, IL, USA). A two-sided P-value < 0.05 was considered statistically significant.

Results

A total of 509 male subjects were included in the present study. Median age was 71 (IQR 67–75) years. Mean total bilirubin level was 7.7 ± 3.5 μmol/L. Baseline characteristics are shown in Table 1, for the whole population and according to tertiles of bilirubin. HDL cholesterol and use of antihypertensive medication, diuretics in particular, and the enzymes ALT and AP were associated with bilirubin concentrations. Age, BMI, physical activity, total energy intake, blood pressure, glucose, total cholesterol, use of lipid lowering medication, indicators of renal function, and the enzyme AST were not related to bilirubin.

In the whole study population, the median M/S ratio was 0.6 (0.5–0.7), the median consumption of legumes, nuts, and seeds was 8 (0–24) g/day, grains and bread 151 (116–196) g/day, meat 108 (85–135) g/day, and dairy products 346 (200–492) g/day. Furthermore, 193 (38%) men adhered to the MDS with more than 4 components. The consumption of components of the MDS, using the medians as cutoffs, and associations of the components of the MDS with total bilirubin levels are shown in Table 2. The eight individual components of the MDS were not significantly related to serum bilirubin levels. In elderly men who adhered to the MDS with more than 4 points, however, bilirubin concentrations were significantly higher (8.2 ± 3.6 versus 7.4 ± 3.4 μmol/L). These results remained unchanged after adjustment for age.

Table 1. Baseline participant characteristics of the study population and according to tertiles of bilirubin concentrations.

	No. of subjects	Study Population	Tertiles of bilirubin			
			I	II	III	*P*-value
N		509	134	202	173	
Bilirubin (μmol/L)	509	7.7 ± 3.5	4.1 ± 1.0	6.9 ± 0.8	11.5 ± 3.1	
Age (years)	509	71 (67–75)	71 (67–75)	71 (67–75)	71 (68–75)	0.58
SES (n low, %)	492	227 (45)	67 (50)	93 (46)	67 (39)	0.088
BMI (kg/m^2)	509	26 ± 3	26 ± 3	26 ± 3	26 ± 3	0.88
Physical Activity	495					
Not active (n, %)		235 (48)	62 (48)	99 (51)	74 (44)	0.71
≤150 METS active (n, %)		124 (25)	31 (24)	45 (23)	48 (28)	
>150 METS active (n, %)		136 (28)	36 (28)	52 (27)	48 (28)	
Total energy intake (Kcal)	509	2276 ± 507	2274 ± 539	2311 ± 508	2237 ± 480	0.38
Systolic blood pressure (mmHg)	509	150 ± 21	151 ± 21	150 ± 19	151 ± 23	0.59
Diastolic blood pressure (mmHg)	509	86 ± 11	85 ± 11	85 ± 11	87 ± 12	0.29

Table 1. (continued)

	No. of subjects	Study Population	Tertiles of bilirubin			
			I	II	III	*P*-value
Use of antihypertensives (n, %)	509	84 (17)	23 (17)	24 (12)	37 (21)	0.046
Beta Blockade (n, %)		45 (9)	12 (9)	14 (7)	19 (11)	0.39
Diuretics (n, %)		50 (10)	16 (12)	10 (5)	24 (14)	0.010
Glucose (mmol/L)	505	6.2 ± 1.4	6.3 ± 1.4	6.2 ± 1.3	6.3 ± 1.5	0.71
Total cholesterol (mmol/L)	509	6.1 (5.4–6.7)	6.2 ± 1.0	6.0 ± 1.0	6.0 ± 1.0	0.39
HDL cholesterol (mmol/L)	509	1.14 ± 0.27	1.07 ± 0.27	1.13 ± 0.27	1.19 ± 0.27	<0.001
Lipid lowering drugs (n, %)	509	2 (0.4)	0 (0)	1 (0.5)	1 (0.6)	0.69
Serum creatinine (μmol/L)	492	104 ± 22	106 ± 23	102 ± 25	103 ± 15	0.30
eGFR (ml/min/1.73m^2)	492	65 ± 13	63 ± 14	66 ± 13	64 ± 11	0.18
Liver function						
AST/SGOT (U/L)	492	8 (7–10)	8 (7–10)	8 (7–9)	8 (7–10)	0.17
ALT/SGPT (U/L)	492	6 (5–10)	8 (6–12)	6 (5–9)	6 (4–9)	<0.001
AP (U/L)	402	36 (30–44)	38 (31–46)	38 (31–44)	34 (29–40)	0.002

SES, Socioeconomic status; BMI, body mass index; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT alanine aminotransferase; AP, alkaline phosphatase.

Furthermore, the associations of different lifestyle components with total bilirubin levels are shown in Table 3. Non-smokers and subjects who consumed > 2 cups of tea per day had higher concentrations of bilirubin, albeit these associations were not statistically significant. Twenty-four percent of the elderly men used wine of which 67% was red wine. Subjects who consumed wine had higher concentrations of bilirubin compared to subjects that did not. Consumption of beer and liquor were not related to bilirubin levels. Results were essentially unchanged after the adjusting these associations for age. In multivariable linear regression analysis that included age, wine, beer, and liquor as determinants of bilirubin, the association of wine with bilirubin levels was confirmed, while beer and liquor were not associated with bilirubin.

Furthermore, we investigated whether the MDS, smoking, consumption of wine and tea were correlated. Wine consumption was positively associated with the MDS ($\chi^2 = 15.12$, $P < 0.001$), and with tea consumption ($\chi^2 = 6.64$, $P = 0.010$). Smoking status was inversely associated with wine consumption ($\chi^2 = 9.7$, $P = 0.002$) and tea consumption ($\chi^2 = 17.02$, $P < 0.001$). The MDS was neither associated with smoking status ($\chi^2 = 0.37$, $P = 0.56$), nor with tea consumption ($\chi^2 = 1.76$, $P = 0.19$).

Table 2. Associations of components of the Mediterranean Diet Score (MDS) with total bilirubin.

	No. of subjects	Median consumption (g/day)	Total Bilirubin	
			Bilirubin (µmol/L)	*P*-value
M/S Fat ratio				
< median	258	0.54 (0.49–0.58)	7.7 ± 3.4	0.84
≥ median	251	0.71 (0.67–0.81)	7.7 ± 3.6	
Legumes, Nuts, seeds				
< median	244	0 (0–3)	7.7 ± 3.6	0.86
≥ median	265	23 (14–33)	7.7 ± 3.5	
Grains, Bread				
< median	247	115 (91–132)	7.7 ± 3.1	0.74
≥ median	262	194 (166–233)	7.8 ± 3.9	
Fruit				
< median	268	111 (49–136)	7.5 ± 3.5	0.11
≥ median	241	269 (225–341)	8.0 ± 3.6	
Vegetables				
< median	249	130 (107–147)	7.6 ± 3.5	0.38
≥ median	260	211 (183–251)	7.8 ± 3.5	
Meat				
≥ median	258	134 (119–158)	7.5 ± 3.3	0.11
< median	251	85 (71–98)	8.0 ± 3.7	
Dairy products				
≥ median	254	492 (413–644)	7.6 ± 3.5	0.36
< median	255	201 (119–262)	7.9 ± 3.5	
Fish				
< median	243	0 (0–6)	7.5 ± 3.8	0.18
≥ median	266	26 (17–38)	7.9 ± 3.2	
MDS				
≤4, low	316		7.4 ± 3.4	0.013
>4, high	193		8.2 ± 3.6	

M/S fat ratio, monounsaturated/saturated fat ratio; MDS, Mediterranean diet score.

Table 3. Associations of lifestyle components with total bilirubin.

		Total Bilirubin	
	No. of subjects	Mean Bilirubin	*P*-value
Tea			
≤ 2 cups	198	7.4 ± 3.1	0.082
>2 cups	311	7.9 ± 3.7	
Wine			
no	388	7.5 ± 3.5	0.012
yes	121	8.4 ± 3.7	
Beer			
no	371	7.7 ± 3.6	0.67
yes	138	7.8 ± 3.4	
Liquor			
no	216	7.6 ± 3.7	0.52
yes	293	7.8 ± 3.4	
Smoking status[a]			
Non-smoker	349	7.9 ± 3.7	0.079
Current smoker	159	7.3 ± 3.1	

[a]*missing data in one subject*

Table 4. Multivariable associations of total bilirubin with its correlates.

	Total Bilirubin								
	Model 1			Model 2			Model 3		
	Beta	SE	*P*-value	Beta	SE	*P*-value	Beta	SE	*P*-value
MDS	0.84	0.32	0.009	0.70	0.32	0.031	0.68	0.32	0.036
Smoking	-0.59	0.34	0.079	-0.41	0.34	0.23			
Wine	0.91	0.36	0.013	0.66	0.37	0.079	0.79	0.37	0.033
Tea	0.58	0.32	0.072	0.40	0.32	0.22			

Unstandardized beta's are shown

Model 1: Crude analysis

Model 2: multivariable model: bilirubin = MDS + smoking + wine + tea

Model 3: multivariable model after stepwise backward elimination: bilirubin = MDS + wine

MDS, Mediterranean Diet Score; SE, standard error

In univariable linear regression analyses (Table 4, model 1), the MDS and wine consumption were positively associated with bilirubin levels. Smoking status and tea consumption were not significantly associated with bilirubin. In a multivariable model with MDS, smoking status, wine, and tea consumption (Table 4, model 2), the MDS was significantly associated with bilirubin. After removing smoking status and tea consumption from the model, the MDS and wine consumption were significantly associated with bilirubin levels (Table 4, model 3). The men who adhered to the MDS and consumed wine had a 1.5 μmol/L (20%) higher bilirubin level compared to the men who did not adhere to the MDS and did not consume wine.

Discussion

In this study we demonstrated that, even though the individual components of the Mediterranean diet were not significantly associated with serum bilirubin concentrations, overall adherence to the Mediterranean diet and wine consumption were significantly associated with higher serum bilirubin concentrations. Although not statistically significant, we found that smoking status was inversely associated with serum bilirubin and that tea consumption was positively associated with bilirubin concentrations in univariable analyses.

The traditional Mediterranean diet incorporates high consumption of fruits, vegetables, legumes, nuts, cereals, fish, unsaturated oils, and low intake of dairy products and red meat (18). Trichopoulou et al. (17) combined the consumption of these food groups into what is known as the MDS. In the present study, significant associations of the individual components with bilirubin were not found, whereas high adherence to the MDS was significantly associated with higher bilirubin levels. Similar positive associations with health have been described in previous studies (17,19). Apparently, small effects of the individual food components may enlarge when the individual food components are combined into a nutritionally adequate dietary pattern score like the MDS (17).

A number of studies have investigated the effects of the Mediterranean diet on oxidative stress (8–10). Dai et al. (8) studied 138 twin pairs and found a 7% decrease in the ratio of reduced to oxidized glutathione, a plasma marker of oxidative stress, per unit increase in the MDS. In addition, Urquiaga et al. (18) showed that adherence to the Mediterranean diet resulted in better antioxidant defenses and less oxidative damage compared to a Western or US diet. In line with these findings, we demonstrate that adherence to the Mediterranean diet is associated with higher concentrations of serum bilirubin, and with a lower level of oxidative stress.

Bilirubin is the end product of heme catabolism. Heme oxygenase-1 (HO-1) splits heme into carbon monoxide, ferrous iron, and biliverdin, which is subsequently reduced to bilirubin by biliverdin reductase (1,20). Since HO-1 is the enzyme that catalyzes the rate-limiting step in heme degradation (21,22), induction of HO-1 could result in higher

levels of end products of heme degradation, including bilirubin. HO-1 is a highly inducible enzyme, influenced by bioactive compounds such as resveratrol, which is commonly found in grapes and red wine (23). In the current study, we found that consumption of wine, which prevailingly consisted of red wine (i.e. 67%), was indeed independently associated with higher bilirubin levels.

Several studies have demonstrated that smoking, a major contributor to oxidative stress (7), is inversely associated with HO-1 activity and bilirubin concentrations. In vitro, over-expression of HO-1 inhibited cigarette smoke-induced cell death (24). Furthermore, mice exposed to cigarette smoke showed elevated expression of HO-1 (24), which results in higher concentrations of bilirubin. Schwertner et al. have shown in humans that serum bilirubin concentrations were inversely related to cigarette smoking (5). In the present study, we found that current smokers had lower bilirubin levels compared to non-smokers, albeit this was not statistically significant. Given the correlations between smoking status, wine consumption, tea consumption and the MDS, it is possible that the association of smoking with bilirubin was confounded by these variables.

This study has several limitations. First, the study population was relatively small and did not include women or middle-aged participants. It remains to be established whether the Mediterranean diet and wine consumption are also associated with bilirubin in these groups. Second, given the observational nature of the current study, cause-effect relationships cannot be ascertained. Finally, because only total bilirubin was measured we were not able to differentiate between direct and indirect bilirubin. A specific strength of this study was the collection of detailed information on the consumption of different food items and alcoholic beverages. In addition, the detailed information about smoking status and different types of alcohol consumption made it possible to study the independent associations of the MDS and wine consumption with bilirubin.

In conclusion, a healthy dietary pattern like the Mediterranean diet and consumption of wine may increase bilirubin levels. High bilirubin levels may have beneficial effects on oxidative stress and subsequent oxidative stress-related diseases. When our findings are confirmed by other studies, the MDS and wine consumption may enhance bilirubin concentrations to protect against oxidative stress.

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